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ORIGINAL ARTICLE

Cardiopulmonary exercise testing for predicting postoperative morbidity in patients undergoing hepatic resection surgery

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Abstract

Objectives: Cardiopulmonary exercise testing (CPET) may predict which patients are at risk for adverse outcomes after major abdominal surgery. The primary aim of this study was to determine whether CPET variables are predicative of morbidity.

Methods: High-risk patients undergoing elective, one-stage, open hepatic resection were preoperatively assessed using CPET. Morbidity, as defined by the Postoperative Morbidity Survey (POMS), was assessed on postoperative day 3.

Results: A total of 104 patients underwent preoperative CPET and were included in the analysis. Of these, 73 patients (70.2%) experienced postoperative morbidity. Oxygen consumption at anaerobic threshold ($\dot{V}_{O_2}$ at AT, ml/kg/min) was the only CPET predictor of postoperative morbidity on multivariable analysis, with an area under the curve (AUC) of 0.66 [95% confidence interval (CI) 0.55–0.76]. In patients requiring a major hepatic resection (three or more segments), a $\dot{V}_{O_2}$ at AT of <10.2 ml/kg/min gave an AUC of 0.79 (95% CI 0.68–0.86) with 83.9% sensitivity and 52.0% specificity, 80.6% positive predictive value and 62.5% negative predictive value.

Conclusions: The application of a cut-off value for $\dot{V}_{O_2}$ at AT of <10.2 ml/kg/min in patients undergoing major hepatic resection may be useful for predicting which patients will experience morbidity.

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Introduction

Advances in hepatic resection surgery have enabled the safe resection of up to 60% of functional liver parenchyma[1] and improved in-hospital mortality rates to <2%.[2,3] However, the substantial physiological insult of this major procedure is associated with high rates of postoperative morbidity in the order of 50–60%.[4,5] The ability to identify patients at risk for postoperative morbidity can inform decision making and support the allocation of resources, including those of postoperative critical care.

Cardiopulmonary exercise testing (CPET) is a method of assessing preoperative cardiopulmonary fitness which has been used successfully to improve the accuracy of preoperative prediction of postoperative complications and mortality.[6–8] In major abdominal surgery, lower oxygen consumption at anaerobic threshold ($\dot{V}_{O_2}$ at AT, ml/kg/min) measured by CPET is associated with increased postoperative morbidity and poorer clinical outcomes.[9–11] However, the role of CPET in predicting morbidity in hepatic resection is unclear. The primary aim of this study was to determine whether CPET-derived variables were associated with short-term morbidity.

Materials and methods

This was a single-centre, prospective cohort study of consecutive patients aged over 18 years who underwent CPET as part of preoperative assessment for elective, one-stage, open hepatic resection at the Royal Marsden National Health Service Foundation Trust between May 2010 and April 2014. Patients considered to be at high risk were referred for CPET. These included patients aged >70 years, patients aged <70 years with cardiorespiratory comorbidities and patients scheduled for hepatic resection involving synchronous bowel resection or vascular reconstruction or extensive biliary resection. The study was approved by the local institutional review board.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed and reported by one of three consultant anaesthetists. Testing was conducted using the standardised approach recommended by the American Thoracic Society and American College of Physicians.[12]

Cardiopulmonary exercise testing was conducted on an electromagnetically braked cycle ergometer (Ultima CardiO$_2$®; Medical Graphics Corp., St Paul, MN, USA) following resting spirometry. Testing consisted of a 3-min rest period, 3 min of freewheeling and then pedalling against a ramped resistance/workload. The workload ramp gradient was determined using an accepted standard technique based on a calculation using predicted freewheel oxygen uptake ($\dot{V}_{O_2}$), predicted $\dot{V}_{O_2}$ at peak exercise, height and age.[12,13] Testing was terminated at the patient's volition, if the patient became symptomatic or if he or she was unable to maintain a cadence rate of 60 revolutions per minute (rpm). A 5-min recovery period was applied after the termination of testing.

Ventilation and gas exchange were measured using a metabolic cart (Geratherm Respiratory GmbH, Love Medical Ltd, Manchester, UK). Heart rate, full 12-lead electrocardiogram (ECG), blood pressure and pulse oximetry were monitored throughout CPET.

The CPET data were analysed using Cardioperfect 1.6.2.1105 [Welch Allyn (UK) Ltd, Aston Abbotts, UK] and MedGraphics BreezeSuite 7.2.0.64SP7 (Medical Graphics Corp.) to derive the following variables: $\dot{V}_{O_2}$ at AT (ml/kg/min); peak $\dot{V}_{O_2}$ (ml/kg/min); ventilatory equivalents for carbon dioxide (CO_2) at AT (VE_{CO_2}), and heart rate at AT (beats/min). The $\dot{V}_{O_2}$ peak was defined as the mean of the highest exertional oxygen uptake achieved over the last 30 s of maximal exercise. The AT was determined using the V-slope method outlined by Wasserman.[13] Values, where appropriate, were indexed to actual body weight. Table S1 (online) provides further explanation of the CPET variables. Results were routinely reviewed and reported by two of the consultant anaesthetists to ensure the validity of all CPET values derived.

Patient population

Baseline patient characteristics recorded for all patients included age, sex, body mass index (kg/m^2), American Society of Anesthesiologists (ASA) score, World Health Organization functional status score,[14] preoperative chemotherapy, history of smoking, type of liver resection determined according to the number of segments resected (minor for less than three segments and major for three or more segments),[15] reason for liver resection and presence of comorbidities.

Outcome measures

Outcomes were recorded by data collection officers blinded to CPET data and not directly involved in the study. Morbidity was measured using the Postoperative Morbidity Survey (POMS)[16] on postoperative day (PoD) 3. The POMS classifies morbidities according to whether they refer to cardiovascular, pulmonary, renal, gastrointestinal, neurological, infectious or haematological occurrences, wound complications or pain.

The primary outcome was the presence of postoperative morbidity defined as a POMS score of ≥1 on PoD 3. Complications were also classed according to the Clavien–Dindo system of classification,[17] but these data were not used in the primary outcome analysis because poor performance on CPET is associated with both postoperative medical and surgical complications and thus it was considered to be more appropriate to assess individual systems as per the POMS. Secondary outcomes measures were length of stay (LoS) in hospital, LoS in the critical care unit (CCU) and readmission to the CCU.

Perioperative management

All patients were admitted to hospital on the day of scheduled surgery. Anaesthesia was provided by one of three consultant anaesthetists and surgery performed by one of two consultant hepatobiliary surgeons. The hepatic resection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Inc., Boulder, CO, USA) and argon beam coagulation. For patients with malignant tumours, the transection plane was first determined by intraoperative ultrasonography and the resection phase was performed under low central venous pressure conditions. There were no protocols for intraoperative management, but patients deemed to be at high risk were given additional cardiac output monitoring. The standard method of postoperative pain management referred to a thoracic epidural, from which the patient was weaned before PoD 3. Postoperative management included the routine admission of all patients to the CCU. A protocalized care package that included early mobilization and commencement of enteral nutrition was applied to all patients.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation or median and interquartile range (IQR), depending on their distribution. Categorical variables are reported as frequencies with percentages. All statistical results are accompanied by 95% confidence intervals (CIs). Non-parametric receiver operating characteristic (ROC) curves were constructed for CPET variables associated with POMS-defined morbidity on PoD 3 to assess their independent ability to discriminate between patients with and without in-hospital postoperative morbidity. Optimal cut-off points were obtained by minimizing the distance between points on the ROC curve and the upper left corner.

Logistic regression analysis was used to assess the independent and multivariable relationships between POMS-defined postoperative morbidity on PoD 3 and predictive variables. Audit data from the study institution indicated that approximately 70% of patients submitted to hepatic resection experienced postoperative POMS-defined morbidity. Seven predictive variables (limited to satisfy the '10 events per variable' rule [18]) were thus identified as likely causal or predictive factors for a multivariable logistic regression model: $\dot{V}_{O_2}$ at AT; $\dot{V}_{O_2}$ peak; VE_{CO_2} at AT; heart rate at AT; extent of liver resection (minor or major); gender, and age. A backward stepwise selection procedure was employed in order to identify a suitable multivariable model. The sensitivity of the selected model to variable exclusion, the inclusion of non-selected variables and two-way interactions was also assessed using the Akaike information criterion (AIC). The Hosmer–Lemeshow goodness-of-fit test was used to assess the adequacy of each logistic regression model. For hospital LoS, Cox regression was used with the same model selection as for the logistic regression analyses. Patients who died were treated as censored for the purposes of analysis.

Categorical comparisons were conducted using the chi-squared test or Fisher's exact test depending on cell number. Non-parametric comparisons were performed using the Mann–Whitney *U*-test. Parametric comparisons were carried out using Student's *t*-test. All analyses were undertaken using STATA Version 12.0 (StataCorp LP, College Station, TX, USA).

Results

A total of 218 patients were scheduled for hepatic resection during the study period, of whom 116 (53.2%) underwent CPET prior to surgery (Fig. 1). There were no complications during the performance of CPET in these 116 patients, although two patients were unable to obtain ATs during CPET and were excluded from analysis. A further 10 patients were also excluded because they did not undergo the intended

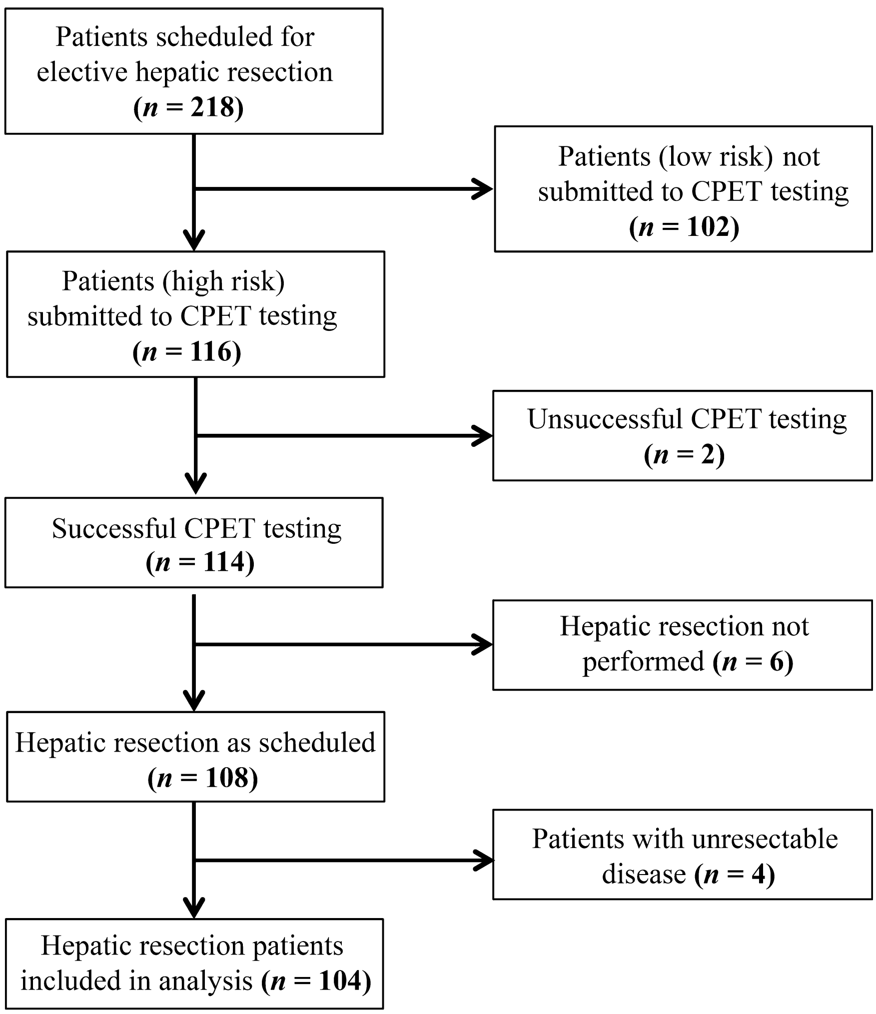

Figure 1 Flow of patients in the study. CPET, cardiopulmonary exercise testing

Table 1 Preoperative demographics and postoperative outcomes in patients submitted to cardiopulmonary exercise testing prior to hepatic resection (n = 104)

Variable	Value
Age, years, median (IQR)	65 (55–70)
Sex ratio (M:F)	60:44
BMI, kg/m^2, median (IQR)	26.4 (24.2–29.5)
Liver disease, n (%)	
Colorectal liver metastasis	82 (78.8%)
Hepatocellular carcinoma	8 (76.9%)
Non-colorectal liver metastasis	3 (2.9%)
Other	11 (10.6%)
ASA score, median (IQR)	2 (2–3)
WHO performance status, n (%)	
WHO 0	45 (43.2%)
WHO 1	54 (51.9%)
WHO 2	4 (3.8%)
WHO 3	1 (1.0%)
Preoperative chemotherapy, n (%)	42 (40.2%)
Comorbidities, n (%)	
COPD	14 (13.4%)
IHD	22 (21.0%)
IDDM	22 (21.2%)
Chronic renal impairment	7 (7.6%)
Liver cirrhosis	9 (8.7%)
Type of surgery, n (%)	
Minor liver resection	65 (62.5%)
Major liver resection	39 (37.5%)
Operating surgeon ratio (A:B)	55:49
Postoperative morbidity, n (%)	
POMS score ≥1 on PoD 3	73 (70.2%)
Dindo–Clavien any grade	70 (65.4%)
Dindo–Clavien Grade III+	25 (24.0%)
Length of stay, days, median (IQR)	
Hospital	9 (7–11)
CCU	2 (1–3)
Readmission to CCU, n (%)	14 (13.5%)
Inpatient mortality, n (%)	2 (1.9%)

ASA, American Society of Anesthesiologists; BMI, body mass index; CCU, critical care unit; COPD, chronic obstructive pulmonary disease; F, female; IDDM, insulin-dependent diabetes mellitus; IHD, ischaemic heart disease; IQR, interquartile range; M, male; PoD, postoperative day; POMS, Postoperative Morbidity Survey; WHO, World Health Organization.

surgery following CPET. Of these, one declined surgery, one died before the planned operation date, four were deemed to be unfit for surgery following a multidisciplinary team decision process and four patients had unresectable disease and underwent open-and-close surgery. In total, 104 patients (60 men and 44 women) underwent CPET followed by the intended hepatic resection and their data were included in the analysis. Table 1 shows patient demographics and perioperative characteristics. Two patients (1.9%) died within 30 days of hepatic resection. The first patient death occurred on PoD 6 and was caused by a myocardial infarction. The second patient death occurred on PoD 12 and was caused by multi-organ failure following an extended right hepatectomy. Table 2 shows a summary of the CPET data measured for all 104 patients included in the analysis.

Table 2 Summary of cardiopulmonary exercise testing (CPET) outcomes in patients undergoing hepatic resection (n = 104)

CPET variable	Median (IQR)
VO_2 AT, ml/kg/min	10.5 (9.2–11.3)
VO2 peak, ml/kg/min	15.5 (12.8–17.6)
VE_{CO_2} AT	32.4 (29.1–37.2)
Workload AT, Watts	58 (28–74)
O_2 pulse AT, ml/beat	7 (6.2–9.1)
Heart rate AT, beats/min	103 (98–111)

AT, anaerobic threshold; IQR, interquartile range.

Postoperative morbidity

Seventy-three patients (70.2%) experienced POMS-defined morbidity on PoD 3. The CPET variables on univariate analysis associated with postoperative morbidity were $\dot{V}O_2$ AT and $\dot{V}_{O_2}$ peak (Table 3). For $\dot{V}_{O_2}$ at AT and the presence of POMS-defined morbidity, the area under the curve (AUC) was 0.66 (95% CI 0.55–0.76; P = 0.026). The optimal cut-off point was 10.2 ml/kg/min, giving sensitivity of 65.3% and specificity of 58.2%, a positive predictive value (PPV) of 64.3% and a negative predictive value (NPV) of 59.2% (Fig. S1, online). The AUC for VO_2 peak and POMS-defined morbidity was 0.60 (95% CI 0.51–0.71; P = 0.048). The optimal cut-off was 15.8 ml/kg/min, giving sensitivity of 69.1% and specificity of 50.0%, with a PPV of 67.9% and NPV of 52.1% (Fig. S2, online).

The proportion of patients experiencing POMS-defined morbidity was significantly higher in patients undergoing major liver resection compared with those undergoing minor liver resection [odds ratio (OR) 2.97 (95% CI 1.90–4.82) and OR 0.41 (95% CI 0.20–0.69), respectively; P = 0.004].

Odds ratios for $\dot{V}_{O_2}$ at AT (OR 1.23, 95% CI 1.02–1.38) and major hepatic resection (OR 2.98, 95% CI 1.97–4.84) were used in a multivariable logistic regression model for predicting postoperative morbidity. When major liver resection was combined with a $\dot{V}_{O_2}$ at AT of <10.2 ml/kg/min, the ability of the model to discriminate which patients would suffer from morbidity had an AUC of 0.79 (95% CI 0.68–0.86), with sensitivity of 83.9%, specificity of 52.0%, a PPV of 80.6% and an NPV of 62.5%, for morbidity on PoD 3 (Fig. 2).

Table 3 Relationships between predictive variables and a Postoperative Morbidity Survey score of ≥1 on postoperative day 3

Variable	Value	Univariable OR (95% CI; *P*-value)	Multivariable OR (95% CI; *P*-value)
$\dot{V}_{O_2}$ AT, ml/kg/min, median (IQR)	10.5 (9.2–11.3)	1.24 (1.03–1.40; 0.022)	1.23 (1.02–1.38; 0.029)
VO_2 peak, ml/kg/min, median (IQR)	15.5 (12.8–17.6)	1.03 (1.01–1.06; 0.044)	
VE_{CO_2} AT, ml/kg/min, median (IQR)	32.4 (29.1–37.2)	1.02 (0.95–1.07; 0.542)	
Heart rate AT, beats/min, median (IQR)	103 (98–111)	1.06 (0.77–1.89; 0.820)	
Age, years, median (IQR)	65 (55–70)	1.01 (0.95–1.07; 0.142)	
Gender, male, *n* (%)	60 (57.7%)	0.97 (0.65–1.76; 0.773)	
Hepatic resection, *n* (%)			
Major	39 (37.5%)	2.97 (1.90–4.82; 0.004)	2.98 (1.97–4.84; 0.003)
Minor	65 (62.5%)	0.41 (0.20–0.69)[a]	

[a]Odds ratio estimates for reference category of minor hepatic resection.
95% CI, 95% confidence interval; AT, anaerobic threshold; IQR, interquartile range; OR, odds ratio.

There were no differences in frequencies of POMS-defined morbidity (P = 0.584) or complications of severity of Clavien–Dindo Grade III or higher (P = 0.238) between patients operated by the two operating surgeons, respectively. Seventy patients (67.3%) experienced complications of any Clavien–Dindo grade and 25 patients (24.0%) experienced complications of Clavien–Dindo Grade III or higher. Major hepatic resection was the only predictive or causal variable associated with complications of Clavien–Dindo Grade III or higher (OR 3.43, 95% CI 2.32–4.78; P = 0.001) (Table S2, online).

Hospital LoS, CCU LoS and critical readmission rates

Major hepatic resection, increasing age and decreasing $\dot{V}_{O_2}$ at AT were independently associated with increased hospital LoS (Table 4). Patients with a higher $\dot{V}_{O_2}$ AT had an increased chance of early discharge [hazard ratio (HR) 1.37, 95% CI 1.13–1.58], whereas patients undergoing major hepatic resection had a decreased chance of early discharge (HR 0.48, 95% CI 0.32–0.67). In the final Cox multivariable model, major hepatic resection (HR 0.46, 95% CI 0.31–0.69) and a decreasing $\dot{V}_{O_2}$ at AT (HR 1.34, 95% CI 1.11–1.52) were associated with later discharge from hospital. Major hepatic resection was also associated with a significantly longer CCU LoS (3 days versus 1 day; P < 0.001) and a higher rate of readmission to the CCU (OR 3.23, 95% CI 2.13–4.52). None of the CPET variables studied were associated with CCU LoS or readmission to the CCU.

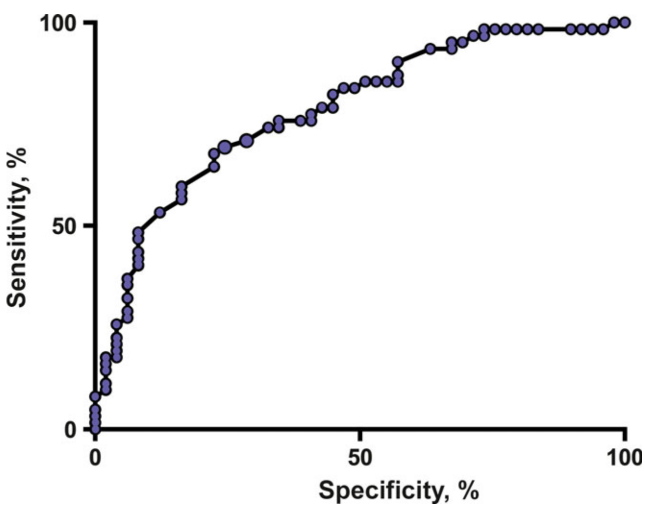

Figure 2 Receiver operating characteristic curve for the multivariable logistic model combining major liver resection and a VO_2 at anaerobic threshold (AT) of <10.15 ml/kg/min for predicting Postoperative Morbidity Survey (POMS)-defined morbidity (area under the curve 0.79, 95% confidence interval 0.69–0.86)

Discussion

The findings of this study show that the only CPET variable associated with postoperative morbidity in high-risk patients undergoing hepatic resection is VO_2 at AT. A VO_2 at AT threshold of <10.2 ml/kg/min is a predictor of POMS-defined morbidity on PoD 3 in patients undergoing major hepatic resection.

Morbidity following major surgery when measured by the POMS most frequently occurs on PoD 3[16] and a score of ≥1 is associated with worse clinical outcomes, including longer hospital LoS.[9–11] The VO_2 at AT threshold derived in this study may be useful for deciding which patients following major hepatic resection will benefit from increased medical resources such as postoperative critical care or critical care outreach services. Although the model has good sensitivity of 83.9% and a PPV of 80.6%, its NPV is 62.5%, which limits its use as a rule-out test. As a result, a significant proportion of patients identified by this model as unlikely to develop morbidity will develop it.

In this study, the moderate capacity of VO_2 at AT in predicting morbidity is in keeping with the literature evaluating

Table 4 Independent and final Cox regression model analysis for predictive variables and hospital length of stay

Variable	Values	Independent HR (95% CI; *P*–value)	Multivariable Cox model (95% CI; *P*–value)
$\dot{V}_{O_2}$ AT, ml/kg/min, median (IQR)	10.5 (9.2–11.3)	1.37 (1.13–1.58; 0.023)	1.34 (1.11–1.52; 0.024)
VO_2 peak, ml/kg/min, median (IQR)	15.5 (12.8–17.6)	1.15 (0.99–1.40; 0.064)	
VE_{CO_2} AT, ml/kg/min, median (IQR)	32.4 (29.1–37.2)	0.97 (0.93–1.02; 0.433)	
Heart rate AT, beats/min, median (IQR)	103 (98–111)	1.01 (0.99–1.02; 0.907)	
Age, years, median (IQR)	65 (55–70)	0.95 (0.91–0.99; 0.044)	
Gender, male, *n* (%)	60 (57.7%)	0.98 (0.98–1.04; 0.786)	
Hepatic resection, *n* (%)			
Major	39 (37.5%)	0.48 (0.32–0.67; 0.002)	0.46 (0.31–0.69; 0.002)
Minor	65 (62.5%)	1.55 (1.22–2.32)[a]	1.52 (1.21–2.34)

[a]Odds ratio estimates for the reference category of minor hepatic resection.
95% CI, 95% confidence interval; AT, anaerobic threshold; HR, hazard ratio; IQR, interquartile range.

CPET variables as risk prediction tools in major abdominal surgery.[11,12,19] Only two studies investigating the use of CPET in predicting outcomes in liver resection surgery have been published. Neither study identified $\dot{V}_{O_2}$ at AT or $\dot{V}_{O_2}$ peak as predictors of postoperative morbidity. Dunne *et al.*[20] prospectively assessed 197 patients who underwent preoperative CPET and found the only variable associated with postoperative morbidity (measured using complications classified by Clavien–Dindo grade) was heart rate at AT (OR 1.02, 95% CI 1.00–1.04). Similar to this study, a higher $\dot{V}_{O_2}$ at AT was associated with a shorter time to discharge from hospital (HR 2.16, 95% CI 1.18–3.96) and the size of the hepatic resection was the most important variable in predicting postoperative morbidity. Junejo *et al.*'s[5] evaluation of CPET in predicting outcomes in hepatic resection surgery is more comparable with this study in that it used a similar number of patients (n = 108), applied CPET in patients considered to be at high risk and used POMS scores to assess morbidity. Unlike this study, Junejo *et al.*[5] found VE_{CO_2} at AT to be the only CPET variable independently associated with postoperative morbidity, with an AUC of 0.65 (95% CI 0.53–0.77). A VE_{CO_2} at AT of ≥34.5 ml/kg/min was found to have specificity of 84% and sensitivity of 47%, with a PPV of 76% and an NPV of 60%, for POMS-defined morbidity.

The limitations of this study include the applicability of its data to high-risk patients only, which was determined by the study's inclusion criteria. Additionally, although the size of the study population is comparative with that in other CPET studies,[5,21] it is small. This limited the number of predictive variables that could be studied in the multivariable analysis. Finally, the fact that CPET data were available to clinicians may have impacted on the perioperative management of patients and thus affected outcomes. The main strength of the study was that data collection was performed prospectively by data collection officers blinded to CPET results using validated measures of morbidity.

In conclusion, a $\dot{V}_{O_2}$ at AT of <10.2 ml/kg/min in patients undergoing major hepatic resection surgery may serve as a useful rule-in parameter for predicting which patients will experience postoperative morbidity.

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Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Receiver operating characteristic (ROC) curves for oxygen uptake at estimated lactate threshold (VO_2 anaerobic threshold) for predicting morbidity (area under the curve 0.66, 95% confidence interval 0.55–0.76).

Figure S2. Receiver operating characteristic (ROC) curves for maximal oxygen consumption (VO_2 peak) for predicting morbidity (area under the curve 0.60, 95% confidence interval 0.50–0.71).

Table S1. Explanation of cardiopulmonary exercise testing variables summarized from Older 2013

Table S2. Univariable analysis of predictive or causal variables and complications classed as Clavien–Dindo Grade III or higher

